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**REMARKS**

Claims 12, 15-24, 26, 27, 39 and 40 are presently pending in the instant application. Claims 24 and 27 are allowed. Claim 23 has been amended to correct for an inadvertent lack of a proper antecedent basis. Claims 1 and 11 are hereby cancelled without prejudice or disclaimer. No new matter has been added.

*Rejections under 35 U.S.C. § 112, first paragraph*

*Enablement*

Claims 12, 15, 16, 19, 20, 26 and 39 stand rejected under 35 U.S.C. § 112, first paragraph for an alleged failure to provide a description sufficient to enable a skilled artisan to practice the claimed invention. Specifically, the Examiner alleges that the specification “does not reasonably provide enablement for a nucleic acid encoding an artemin amino acid sequence which is at least 88% identical to SEQ ID NO:26.”

The Examiner alleges that a single amino acid change can alter the function of the protein. While this is true in rare instances, such as in sickle cell anemia, this is not necessarily true in general. In the present case, Applicants disclose several amino acid sequences of mature human and mouse artemin, such as SEQ ID NOS:3, 4,5 and SEQ ID NO:34, 35, and 36, respectively. These sequences have amino acid changes, but yet they still encode the mature artemin, and they retain the function of mature artemin.

The specification also provide assays to determine whether the polypeptides promotes survival in neurons. *See e.g.* Examples 4 (superior cervical ganglia), 5 (NBL-S neuroblastoma), and 6 (dopaminergic neurons). A skilled artisan can apply the assay without undue experimentation to determine the polypeptides that promote survival in neurons.

The claims require that the claimed polynucleotides have a common function; that is, they encode artemin amino acid sequences that promote survival of neurons. A skilled artisan would reasonably expect that an amino acid sequence that is at least 88% identical to SEQ ID NO:26 and that promote survival of neurons would be an artemin. The limitations, “at least 88% identical to SEQ ID NO:26” and “promote survival of neurons”, ensure that any substitutions, deletions, insertions and/or additions in artemin would be minor and would not affect the overall novel feature of the claimed invention. Because artemin shares less than 50% sequence identity to other GDNF family members, it is highly unlikely that other random sequences would meet the limitation of the claims. The specification reasonably enables a person of ordinary skill in the art to practice the claimed invention at the time of filing. Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

*Rejections under 35 U.S.C. § 112, first paragraph*

*Written Description*

Claims 12, 15, 16, 19, 20, 26 and 39 stand rejected under 35 U.S.C. § 112, first paragraph, for an alleged failure to provide a description “in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.” Specifically, the Examiner alleges that:

These are genus claims. The claims are drawn to a nucleic acid encoding an artemin amino acid sequence which is at least 88% identical to SEQ ID NO:26. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice...sufficient to show the applicant was in possession of the claimed genus.... Thus, no identifying characteristics or properties of the instant polynucleotides are provided such that one skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Applicants respectfully traverse. The specification sufficiently describes a representative number of species in the claimed genus. SEQ ID NO:26 represents the human pre-pro-artemin

polypeptides. First, the specification discloses SEQ ID NO:29, which represents the murine pre-pro-artemin. Human artemin and murine artemin share about 88% sequence identity. (Table 1, at p. 18 of the specification). Second, the specification discloses SEQ ID NOs: 3 (mature human artemin), 4 (mature human artemin), and 5 (mature human artemin), 32 (alternative spliced artemin), 34 (mature murine artemin), 35 (mature murine artemin), 36 (mature murine artemin), and 40 (human pro-artemin). These sequences share at least 88% identity to SEQ ID NO:26. These polypeptide sequences sufficiently represent the genus of sequences that are at least 88% identical to SEQ ID NO:26. Please see the enclosed sequence alignments. (Exhibit A). Examples 4 (superior cervical ganglia), 5 (NBL-S neuroblastoma), and 6 (dopaminergic neurons) in the specification of the present application teach assays to determine whether the polypeptides promotes survival in neurons. Further, the nucleic acid sequences that encode SEQ ID NOs: 26, 29, 3, 4, 5, 34, 35, 36, and 40 are identified by SEQ ID NOs: 24, 27, 6, 7, 8, 37, 38, 39, and 42, respectively. SEQ ID NOs: 30 and 46 also encode SEQ ID NO:26. These nucleic acid sequences sufficiently represent the claimed genus.

The claimed genus is consistent with Example 11 of the Written Description Guidelines, in which the applicant claims “a genus of DNAs that encode amino acid sequence SEQ ID NO:2, *i.e.*, all sequences degenerately related by a genetic code table to SEQ ID NO:1. Although only one species within the genus is disclosed, SEQ ID NO:1, a person of skill in the art could readily envision all the DNAs degenerate to SEQ ID NO:1 by using a genetic code table.” This claim satisfy the written description requirement. In the present application, several species within the genus are disclosed. A skilled artisan can readily envision the cloning of the claimed nucleic acids into expression vectors and the expression of the nucleic acids into the polypeptides that promote survival in neurons.

Example 14 of the Written Description Guidelines suggests that the disclosure of all the variants with “substitutions, deletions, insertions and additions” is not required to satisfy the written description requirement. In Example 14, the variants must have at least 95% identity to a specific SEQ ID NO and can catalyze the reaction A → B. The specification provided an assay

for identifying these variants. Moreover, the Official Guidelines for Written Description Requirement stated, at comment 9, that “there is no basis for a *per se* rule requiring disclosure of complete DNA sequences or limiting DNA claims to only the sequence disclosed.” Accordingly, Applicants need not describe all the species within the genus to satisfy the written description requirement for the genus. The disclosed sequences sufficiently represent the claimed genus. Applicants respectfully request withdrawal of this rejection.

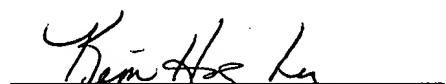
*Rejections under 35 U.S.C. § 112, second paragraph*

Claim 23 stand rejected under 35 U.S.C. § 112, second paragraph, for an alleged failure to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner alleges that the phrase “said artemin amino acid” lacks sufficient antecedent basis. Claim 23 has been amended to recite “said polypeptide” in lieu of “said artemin amino acid”. There is proper antecedent basis for “said polypeptide”.

CONCLUSION

Applicants believe that they have overcome or obviated all of the Examiner’s rejections and objections. Applicants submit that the application is in proper condition for allowance and respectfully request that such allowance be granted.

Respectfully submitted,

  
\_\_\_\_\_  
Kimberly H. Lu, Reg. No. 51,973  
Thompson Coburn LLP  
One US Bank Plaza  
St. Louis, Missouri 63101  
Telephone: 314-552-6307  
Fax: 314-552-7307



**PENDING CLAIMS**

1. (cancelled) An isolated and purified growth factor comprising an artemin amino acid sequence or a conservatively substituted variant thereof or a fragment thereof of at least 8 contiguous amino acids.
2. (previously cancelled) The isolated and purified growth factor of claim 1 which promotes survival of trigeminal ganglion neurons, nodose ganglion neurons, superior cervical ganglion neurons, and tyrosine-hydroxylase-expressing dopaminergic ventral midbrain neurons.
3. (previously cancelled) The isolated and purified growth factor of claim 1 comprising a mammalian sequence which is at least 75% identical to SEQ ID NO:19, SEQ ID NO:33 or a conservatively substituted variant thereof.
4. (previously cancelled) The isolated and purified growth factor of claim 3 comprising a human polypeptide sequence as set forth in SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO:5.
5. (previously cancelled) The isolated and purified growth factor of claim 4 comprising a human pro-artemin as set forth in SEQ ID NO:40 or a human pre-pro-artemin as set forth in SEQ ID NO:26 or SEQ ID NO:32 or a conservatively substituted variant thereof or a polypeptide comprising a non-artemin pre-pro- region and the human polypeptide sequence.
6. (previously cancelled) The isolated and purified growth factor of claim 3 comprising a mouse polypeptide sequence as set forth in SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36 or a conservatively substituted variant thereof.
7. (previously cancelled) The isolated and purified growth factor of claim 6 comprising a mouse pro-artemin as set forth in SEQ ID NO:41 or a mouse pre-pro-artemin as set forth in SEQ ID NO:27 or a conservatively substituted variant thereof or a polypeptide comprising a non-artemin pre-pro- region and the mouse polypeptide.

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8. (previously cancelled) The isolated and purified growth factor of claim 1 comprising an amino acid sequence identical to the artemin polypeptide encoded by the human cDNA contained in the DNA deposited with ATCC on December 22, 1998.

9. (previously cancelled) The isolated and purified growth factor of claim 1 comprising an artemin polypeptide produced by a process comprising the steps of:

- (a) transforming a host cell with human artemin cDNA clone deposited with ATCC on December 22, 1998 operably linked to expression regulatory elements and
- (b) expressing artemin polypeptide encoded by the clone.

10. (previously cancelled) An isolated and purified polypeptide comprising:

- (a) a pre- region of human artemin as set forth in SEQ ID NO:48 or a pre- region of mouse artemin as set forth in SEQ ID NO:49,
- (b) a pro- region of human artemin as set forth in SEQ ID NO:50 or a pro- region of mouse artemin as set forth in SEQ ID NO:51,
- (c) a pre-pro- region of human artemin as set forth in SEQ ID NO:52 or a pre-pro- region of mouse artemin as set forth in SEQ ID NO:53, or
- (d) a conservatively substituted variant of (a), (b) or (c).

11. (cancelled) A pan-growth factor comprising the artemin polypeptide fragment of claim 1 and a fragment of at least one other growth factor from the TGF- $\beta$  superfamily.

12. (previously amended—6 times) An isolated polynucleotide encoding a pan-growth factor which polynucleotide comprises a nucleotide sequence encoding an artemin amino acid sequence that has biological activity of artemin, wherein said nucleotide sequence comprises not more than 10,000 nucleotides, and wherein said artemin amino acid sequence is at least 88% identical to SEQ ID NO:26, and wherein said amino acid sequence promotes survival of neurons, and wherein said polynucleotide also comprises a nucleotide sequence encoding a polypeptide containing an active domain of at least one other growth factor from the TGF- $\beta$  superfamily.

13. (previously cancelled) A composition comprising the growth factor of claim 1 and a GFR $\alpha$  polypeptide.

14. (previously cancelled) The composition of claim 13 wherein the GFR $\alpha$  polypeptide is a GFR $\alpha$ 3 polypeptide or a GFR $\alpha$ 1 polypeptide.

15. (previously amended—6 times) An isolated nucleic acid molecule comprising no more than 10,000 nucleotides, wherein said nucleic acid molecule encodes an artemin amino acid sequence that has biological activity of artemin, and wherein said artemin amino acid sequence is at least 88% identical to SEQ ID NO:26, and wherein said artemin amino acid sequence promotes survival of neurons.

16. (original) The isolated and purified nucleic acid molecule of claim 15, wherein the artemin polypeptide promotes survival of trigeminal ganglion neurons, nodose ganglion neurons, superior cervical ganglion neurons, and tyrosine-hydroxylase-expressing dopaminergic ventral midbrain neurons.

17. (previously amended—2 times) The isolated and purified nucleic acid molecule of claim 15 comprising a nucleotide sequence encoding an artemin polypeptide comprising SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:19, SEQ ID NO:34, SEQ ID NO:35 or SEQ ID NO:36.

18. (original) The isolated and purified nucleic acid molecule of claim 17 comprising a nucleotide sequence as set forth in SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39 or SEQ ID NO:44.

19. (original) A vector comprising expression regulatory elements operably linked to the nucleic acid molecule of claim 15.

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20. (original) A host cell transformed with the vector of claim 19.

21. (original) The isolated and purified nucleic acid molecule of claim 15 comprising ATCC deposit number 203559 made on December 22, 1998.

22. (original) A host cell transformed with the vector of claim 21.

23. (currently amended—4 times) An isolated and purified nucleic acid molecule comprising no more than 10,000 nucleotides, wherein said nucleic acid molecule encodes a polypeptide selected from the group consisting of SEQ ID NOS: 3, 4, 5, 26, 29, 32, 33, 34, 35, 40, and 41, wherein said [artemin amino acid sequence] polypeptide promotes survival of neurons.

24. (original) The isolated and purified nucleic acid molecule of claim 23 comprising a human pro-artemin nucleotide as set forth in SEQ ID NO:42, a human pre-pro-artemin nucleotide as set forth in SEQ ID NO:24, SEQ ID NO:30 or SEQ ID NO:44, a mouse pro-artemin nucleotide as set forth in SEQ ID NO:43, or a mouse pre-pro-artemin nucleotide as set forth in SEQ ID NO:27.

25. (previously cancelled) An isolated nucleic acid molecule comprising an artemin nucleotide sequence, wherein the artemin nucleotide sequence encodes a naturally occurring artemin amino acid sequence selected from the group consisting of a pre-pro-artemin polypeptide, a pro-artemin polypeptide, a mature artemin polypeptide and a fragment of said pre-pro-artemin amino acid sequence that is biologically equivalent to artemin, wherein said fragment has at least 8 contiguous amino acids, and wherein the artemin amino acid sequence is at least 88% identical to SEQ ID NO:26 and wherein said amino acid sequence promotes survival of neurons.

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26. (original) An antisense oligonucleotide which is complementary to the nucleic acid molecule of claim 15.

27. (previously amended—4 times) An isolated nucleic acid molecule comprising a polynucleotide encoding:

- (a) a pre- region of artemin as set forth in SEQ ID NO:54 or SEQ ID NO:55;
- (b) a pro- region of artemin as set forth in SEQ ID NO:56 or SEQ ID NO:57; or
- (c) a pre-pro- region of artemin as set forth in SEQ ID NO:58 or SEQ ID NO:59.

28. (previously cancelled) An isolated and purified antibody which specifically reacts with the artemin polypeptide or fragment of claim 1.

29. (previously cancelled) A method for detecting expression of an artemin polypeptide in a sample comprising contacting the sample with an antibody according to claim 28 and detecting binding of the antibody to the artemin polypeptide.

30. (previously cancelled) A method for detecting expression of an artemin mRNA in a sample which comprises detecting a polynucleotide in the sample that specifically hybridizes to a polynucleotide consisting of SEQ ID NO:9.

31. (previously cancelled) The method of claim 30, wherein detecting the polynucleotide comprises:

- (a) contacting mRNA of the sample with a polynucleotide that specifically hybridizes to a polynucleotide consisting of SEQ ID NO:6; and
- (b) detecting the existence of a hybridization complex between the polynucleotide and the artemin mRNA.

32. (previously cancelled) The method of claim 30, wherein the detecting step comprises:

- (a) producing a cDNA from the artemin mRNA using the reverse transcription method;

(b) contacting the cDNA with at least two oligonucleotides that specifically hybridize to the cDNA to define a region of the cDNA to be amplified;

(c) amplifying the cDNA region; and

(d) detecting the amplified cDNA region.

33. (previously cancelled) A method for providing trophic support to and/or for producing differentiation of a cell comprising treating the cell with an effective amount of an artemin polypeptide or fragment thereof.

34. (previously cancelled) The method of claim 33, wherein the treating step comprises administering to the cell the artemin polypeptide or fragment with or without a GFR $\alpha$ 3 polypeptide.

35. (previously cancelled) The method of claim 33, wherein the target cell is within a patient and the treating step comprises administering to the patient the artemin polypeptide or fragment with or without a GFR $\alpha$ 3 polypeptide.

36. (previously cancelled) The method of claim 33, wherein the target cell is within a patient and the treating step comprises administering to the patient a polynucleotide encoding the artemin polypeptide or fragment.

37. (previously cancelled) The method of claim 33, wherein the artemin polypeptide is expressed by a cell implanted into the patient.

38. (previously cancelled) The method of claim 33, wherein the target cell is a neuron in a patient suffering from peripheral neuropathy, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, ischemic stroke, acute brain injury, acute spinal chord injury, a nervous system tumor such as neuroblastomas, multiple sclerosis, infection or an enteric disease such as idiopathic constipation or constipation associated with Parkinson's

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disease, spinal cord injury or use of opiate pain-killers or the target cell is a non-neuronal cell in a patient suffering from small cell lung carcinoma.

39. (previously added) The polynucleotide according to claim 12, wherein the at least one other growth factor from the TGF- $\beta$  superfamily is selected from the group consisting of transforming growth factor- $\beta$ 1 (TGF $\beta$ 1), transforming growth factor- $\beta$ 2 (TGF $\beta$ 2), transforming growth factor- $\beta$ 3 (TGF $\beta$ 3), inhibin  $\beta$  A (INH $\beta$ A), inhibin  $\beta$  B (INH $\beta$ B), the *nodal* gene (NODAL), bone morphogenetic proteins 2 and 4 (BMP2 and BMP4), the *Drosophila decapentaplegic* gene (*dpp*), bone morphogenetic proteins 5-8 (BMP5, BMP6, BMP7 and BMP8), the *Drosophila* 60A gene family (60A), bone morphogenetic protein 3 (BMP3), the *Vg1* gene, growth differentiation factors 1 and 3 (GDF1 and GDF3), dorsalin (drsln), inhibin  $\alpha$  (INH $\alpha$ ), the *MIS* gene (MIS), growth factor 9 (GDF-9), glial-derived neurotrophic growth factor (GDNF), neurturin (NTN) and persephin.

40. (previously added) The isolated and purified nucleic acid molecule of claim 17 comprising a nucleotide sequence encoding an artemin polypeptide as set forth in SEQ ID NO:19.

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Alignment Report of Untitled ClustallW (Slow/Accurate, Gomnet)  
 Thursday, July 03, 2003 8:52 AM

**Exhibit  
A**

Page 1

|   |            |
|---|------------|
| M E L G L G G L S T L S H C P W P R R Q P A L W P T L A A L L S S V A E A S               | Majority   |
| 1 -         | 7996 SIN3  |
| 1 M E L G L G G L S T L S H C P W P R R Q P A L W P T L A A L L S S V A E A S             | 7996 SIN26 |
| <b>L G S A P R S P A P R E G P P P V L A S P A G H L P G G R T A R W C S S G R A R R</b>  | Majority   |
| 1 -         | 7996 SIN3  |
| 1 L G S A P R S P A P R E G P P P V L A S P A G H L P G G R T A R W C S S G R A R R       | 7996 SIN26 |
| <b>P P P Q P S R P A P P P A P P S A L P R G G R A A R A G G P G S R A R A A G A</b>      | Majority   |
| 1 -         | 7996 SIN3  |
| 1 P P P Q P S R P A P P P A P P S A L P R G G R A A R A G G P G S R A R A A G A           | 7996 SIN26 |
| <b>R G C R L R S Q L V P V R A L G L G H R S D E L V R F R F C S G S C R R A R S P</b>    | Majority   |
| 130 -       | 160        |
| 140 -       | 160        |
| 150 -       | 160        |
| <b>17 R G C R L R S Q L V P V R A L G L G H R S D E L V R F R F C S G S C R R A R S P</b> | 7996 SIN3  |
| 121 R G C R L R S Q L V P V R A L G L G H R S D E L V R F R F C S G S C R R A R S P       | 7996 SIN26 |
| <b>H D L S L A S L L G A G A L R P P P G S R P V S Q P C C R P T R Y E A V S F M D</b>    | Majority   |
| 170 -       | 200        |
| 180 -       | 200        |
| 190 -       | 200        |
| 200 -       | 200        |
| 57 H D L S L A S L L G A G A L R P P P G S R P V S Q P C C R P T R Y E A V S F M D        | 7996 SIN3  |
| 161 H D L S L A S L L G A G A L R P P P G S R P V S Q P C C R P T R Y E A V S F M D       | 7996 SIN26 |

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Alignment Report of Untitled ClustalW (Slow/Accurate, Gonnet)  
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Page 2

| V | N | S | T | W | R | T | V | D | R | L | S | A | T | A | C | G | C | L | G |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

210

220

Majority

|    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 97 | V | N | S | T | W | R | T | V | D | R | L | S | A | T | A | C | G | C | L | G |
|----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

7996 SIN3  
7996 SIN26

Decoration 'Decoration #1': Box residues that differ from the Consensus.

Percent Identity

| Divergence | 1   | 2     |   |
|------------|-----|-------|---|
| 1          |     | 100.0 | 1 |
| 2          | 0.0 |       | 2 |
|            | 1   | 2     |   |

7996 SIN3  
7996 SIN26

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## Alignment Report of Untitled ClustalW (Slow/Accurate, Gonnet)

Page 1

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M E L G L G G L S T L S H C P W P R Q P A L W P T L A A L A L L S S V A E A S Majority

1  
- - - -  
10 20 30 40  
- - - -  
7996 SIN34

| L | G | S | A | P | R | S | P | A | P | E | G | P | P | P | V | L | A | S | P | A | G | H | L | P | G | G | R | T | A | R | W | C | S | G | R    | A     | R | R | Majority |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|------|-------|---|---|----------|
| 1 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 7996 | SIN34 |   |   |          |

R G C R L R S Q L V P V S A L G L G H S S D E L V R F R F C S G S C R R A R S Q Majority

|     |   |      |       |
|-----|---|------|-------|
| 14  | R G C R L R S Q L V P V S A L G L G H S S D E L I R F R F C S G S C R R A R S Q | 7996 | SIN34 |
| 121 | R G C R L R S Q L V P V R A L G L G H R S D E L V R F R F C S G S C R R A R S P | 7996 | SIN26 |

H D L S L A S L L G A G A L R S P P G S R P V S Q P C C R P T R Y E A V S F M D Majority

170  
180  
190  
200

54 HDLSSLGAGALRSPPGSRPISQPCCRPTRYEAVSFMD 7996 SIN34  
161 HDLSSLGAGALRPPGSRPVSQPCCRPTRYEAVSFMD 7996 SIN26



Alignment Report of Untitled ClustalW (Slow/Accurate, Gonnet)

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Page 2

| V | N | S | T | W | R | T | V | D | H | L | S | A | T | A | C | G | C | L | G |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

210

220

Majority

| 94 | V | N | S | T | W | R | T | V | D | H | L | S | A | T | A | C | G | C | L | G |
|----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

7996 SIN34  
7996 SIN26

| 201 | V | N | S | T | W | R | T | V | D | R | L | S | A | T | A | C | G | C | L | G |
|-----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|-----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

Decoration 'Decoration #1': Box residues that differ from the Consensus.

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Divergence

|   | 1          | 2          |   |
|---|------------|------------|---|
| 1 | [redacted] | 88.5       | 1 |
| 2 | 12.5       | [redacted] | 2 |
|   | 1          | 2          |   |

7996 SIN34  
7996 SIN26

Percent Identity



**Alignment Report of Untitled ClustalW (Slow/Accurate, Gonnet)**

Page 1

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|   |              |
|---|--------------|
| M E L G L G G L S T L S H C P W P R Q P A L W P T L A A L L S S V A E A S         | Majority     |
| 10  | 20           |
| 20  | 30           |
| 30  | 40           |
| - - - - -   | S 7996 SIN40 |
| 1 M E L G L G G L S T L S H C P W P R Q P A L W P T L A A L L S S V A E A S       | 7996 SIN26   |
| L G S A P R S P A P R E G P P P V L A S P A G H L P G G R T A R W C S G R A R R   | Majority     |
| 50  | 60           |
| 60  | 70           |
| 70  | 80           |
| 2 L G S A P R S P A P R E G P P P V L A S P A G H L P G G R T A R W C S G R A R R | 7996 SIN40   |
| ● L G S A P R S P A P R E G P P P V L A S P A G H L P G G R T A R W C S G R A R R | 7996 SIN26   |
| P P P Q P S R P A P P P A P P S A L P R G G R A A R A G G P G S R A R A G A       | Majority     |
| 90  | 100          |
| 100   | 110          |
| 110   | 120          |
| 42 P P P Q P S R P A P P P A P P S A L P R G G R A A R A G G P G S R A R A G A    | 7996 SIN40   |
| 81 P P P Q P S R P A P P P A P P S A L P R G G R A A R A G G P G S R A R A G A    | 7996 SIN26   |



●

|   |            |
|---|------------|
| R G C R L R S Q I V P V R A L G L G H R S D E L V R F R F C S G S C R R A R S P     | Majority   |
| 130   | 140        |
| 140   | 150        |
| 150   | 160        |
| 82 R G C R L R S Q I V P V R A L G L G H R S D E L V R F R F C S G S C R R A R S P  | 7996 SIN40 |
| 121 R G C R L R S Q I V P V R A L G L G H R S D E L V R F R F C S G S C R R A R S P | 7996 SIN26 |
| ● H D L S L A S L L G A G A L R P P P G S R P V S Q P C C R P T R Y E A V S F M D   | Majority   |
| 170   | 180        |
| 180   | 190        |
| 190   | 200        |

●

|   |            |
|---|------------|
| 122 H D L S L A S L L G A G A L R P P P G S R P V S Q P C C R P T R Y E A V S F M D | 7996 SIN40 |
| 161 H D L S L A S L L G A G A L R P P P G S R P V S Q P C C R P T R Y E A V S F M D | 7996 SIN26 |



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Alignment Report of Untitled ClustalW (Slow/Accurate, Gonnet)

Page 2

Thursday, July 03, 2003 9:05 AM

| V   | N | S | T | W | R | T | V | D | R | L | S | A | T | A | C | G | C | L | G |   |
|-----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 162 | V | N | S | T | W | R | T | V | D | R | L | S | A | T | A | C | G | C | L | G |
| 201 | V | N | S | T | W | R | T | V | D | R | L | S | A | T | A | C | G | C | L | G |

Majority  
210  
220  
7996 SIN40  
7996 SIN26

Thursday, July 03, 2003 9:05 AM

## Percent Identity

| Divergence | 1     | 2 |   |
|------------|-------|---|---|
| 1          | 100.0 |   | 1 |
| 2          | 0.0   | 2 |   |
|            | 1     | 2 |   |

7996 SIN40  
7996 SIN26

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## Alignment Report of Untitled ClustalW (Slow/Accurate, Gonnet) Thursday, July 03, 2003 9:07 AM

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M P G L I S A R G Q P L L E V G P P Q A H L G G L S L L S A C L G L S A Q P A L Majority

|   |   |      |       |
|---|---|------|-------|
| 1 | M P G L I S A R G Q P L L E V L P P Q A H L G A L F L P E A P L G L S A Q P A L | 7996 | SIN32 |
| 1 | - - - - - M E L G - - - L G G L S T L S H C P W P R R Q P A L                   | 7996 | SIN26 |

W P T L A A L L S S V A E A S L G S A P R S P A P R E G P P P V L A S P A G Majority

- 50 -  
- 60 -  
- 70 -  
- 80 -

W P T L A A L L S S V A E A S L G S A P R S P A P K E G F F V L A S F A G 1996 SIN326  
H L P G G R T A R W C S G R A R R P P P Q P S R P A P P P A P P S A L P R G G Majority

81 H L P G G R T A R W C S G R A R R P P P Q P S R P A P P P A P P S A L P R G G 7996 SIN32  
64 H L P G G R T A R W C S G R A R R P P P O P S R P A P P P A P P S A L P R G G 7996 SIN26

R A A R A G G P G S R A R A A G A R G C R L R S Q L V P V R A L G L G H R S D E Majority

130 140 150 160

121 R A A R A G G P G S R A R A A G A R G C R L R S Q L V P V R A L G L G H R S D E 7996 SIN32  
104 R A A R A G G P G S R A R A A G A R G C R L R S Q L V P V R A L G L G H R S D E 7996 SIN26

L V R F R F C S G S C R R A R S P H D L S L A S L L G A G A L R P P P G S R P V Majority

170  
180  
190  
200

161 L V R F R F C S G S C R R A R S P H D L S L A S L L G A G A L R P P P G S R P V 7996 SIN32  
144 L V R F R F C S G S C R R A R S P H D L S L A S L L G A G A L R P P P G S R P V 7996 SIN26

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## Alignment Report of Untitled CustallW (Slow/Accurate, Gonnet)

Page 2

Thursday, July 03, 2003 9:07 AM

| S | Q | P | C | C | R | P | T | R | Y | E | A | V | S | F | M | D | V | N | S | T | W | R | T | V | D | R | L | S | A | T | A | C | G | C | L | G |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

Majority

210

220

230

201 S Q P C C R P T R Y E A V S F M D V N S T W R T V D R L S A T A C G C I G  
184 S Q P C C R P T R Y E A V S F M D V N S T W R T V D R L S A T A C G C I G

7996 SIN32  
7996 SIN26

Decoration 'Decoration #1': Box residues that differ from the Consensus.

Thursday, July 03, 2003 9:07 AM

Percent Identity

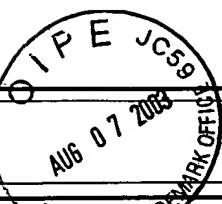
| Divergence | 1    | 2 |            |
|------------|------|---|------------|
| 1          | 91.4 | 1 | 7996 SIN32 |
| 2          | 7.2  | 2 | 7996 SIN26 |
|            | 1    | 2 |            |

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08-11-03

GP/1646

**TRANSMITTAL LETTER  
(General – Patent Pending)**Docket No.  
56029/7996

In Re Application Of:

Millbrandt et al.

Serial No.  
09/220,920Filing Date  
12/24/98Examiner  
Murphy, Joseph F., Ph.D.Group Art Unit  
1646

Title:

Artemin, A Neurotrophic Factor

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Transmitted herewith is:

- Response to Office Action of July 9, 2003 with Exhibit A
- Postcard

in the above identified application.

- No additional fee is required.
- A check in the amount of \_\_\_\_\_ is attached.
- The Commissioner is hereby authorized to charge and credit Deposit Account No. 20-0823 as described below. A duplicate copy of this sheet is enclosed.
- Charge the amount of \_\_\_\_\_
- Credit any overpayment.
- Charge any additional fee required.

  
\_\_\_\_\_  
Signature

Dated: August 7, 2003

Kimberly H. Lu, Reg. #51973  
Thompson Coburn LLP  
One US Bank Plaza, Suite 3500  
St. Louis, Missouri 63101  
314-552-6307

cc: Customer No. 021888

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